

REMARKS

In response to the Office Action mailed August 4, 2006, Applicants have amended claims 1, 4, 24 and 25 and canceled claims 2 and 20. It is urged that support for all the above amendments may be found throughout the specification as originally filed, for example at page 16, lines 14-24. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1, 3-19, and 21-25 are pending in the application. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Claim Rejections – 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In particular, in the Action the PTO asserts that the specification, while being enabling for reducing an ischemia-reperfusion injury, does not reasonably provide enablement for preventing an ischemia-reperfusion injury.

Without acquiescing to the rejection, Applicants have amended the claims to remove recitation of “preventing” an ischemia-reperfusion injury. This amendment is made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Applicants submit that the rejection has been obviated and may be properly withdrawn.

Claim Rejections – 35 U.S.C. § 102

Claims 1-7, 14, 15, 17, 18, 24 and 25 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Singh (U.S. Patent No. 5,912,019). In particular, the PTO asserts that Singh discloses a method of minimizing ischemic insult to an organ (including brain) or skeletal tissue of a subject comprising contacting the organ or tissue with an inhibitor of iNOS (*e.g.*, NAC) and that a preferred dosage is from about 100 to about 300 mg/kg body weight. The PTO

notes that it is not equipped to determine whether the concentration range disclosed by Singh results in a serum concentration of the scavenger claimed by Applicants. It is the PTO's position that the disclosed dosage range reads upon the claimed concentration range and shifts the burden to Applicants to demonstrate otherwise.

Applicants respectfully traverse the rejection on the following grounds. Applicants note that claim 1 has been amended without prejudice or acquiescence to recite "a method for reducing an ischemia-reperfusion injury, comprising administering to a subject in need thereof an effective amount of a free radical scavenger intra-arterially or intravenously prior to, concurrently with, or following reperfusion, wherein the free radical scavenger is administered in a single high dose in an amount sufficient for the serum concentration of the scavenger to be at least 1.5 mM." Applicants submit that Singh does not teach administering a single high dose of free radical scavenger such that the serum concentration is at least 1.5 mM. As described in Applicants' specification as filed at page 16, lines 12-13 "...whereas when administrated at 400 mg/kg or 1000 mg/kg, serum NAC concentrations were about 1.5 mM and 10 mM, respectively." Accordingly, Applicants submit that the highest dose disclosed by Singh (300 mg/kg) would result in a serum concentration of less than 1.5 mM. Therefore, the dosage disclosed by Singh does not read on the concentration of free radical scavenger as recited in the amended claims. As such, Applicants submit that the invention as presently claimed is not anticipated by Singh. Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-25 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Singh (U.S. Patent No. 5,912,019) in view of Andersen (Perfusion 1995, 10:21-26). In particular, the PTO asserts in the Action, as noted above, that Singh discloses a method of minimizing ischemic insult to an organ (including brain) or skeletal tissue of a subject comprising contacting the organ or tissue with an inhibitor of iNOS (e.g., NAC) and that a preferred dosage is from about 100 to about 300 mg/kg body weight. The PTO concedes that Singh does not expressly teach a method wherein the injury is a cerebral injury, cognitive

dysfunction or cerebral hemorrhage or wherein the injury is associated with cardiopulmonary bypass procedure. The PTO relies on Andersen to make up this deficiency. In particular, the PTO asserts, *inter alia*, that Andersen teaches the role of NAC administration during cardiopulmonary bypass and that NAC can be used alone or in conjunction with other therapies which aim to minimize reperfusion injuries. Further, the PTO alleges that the adjustment of particular working conditions including the amount of free radical scavenger administered is merely a matter of routine optimization.

Applicants respectfully traverse the rejection and submit that the references, taken for what they teach as a whole, do not obviate the presently claimed invention. The PTO fails to establish a *prima facie* case of obviousness. (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness).) The Examiner must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355, 47 USPQ2d 1453 (Fed. Cir. 1998).)

At the time of filing the present application, the cited combination of references would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with the requisite reasonable expectation of success. In particular, Applicants submit that their invention centers in part on the discovery that "...a single high dose of NAC (400-1000 mg/kg) was surprisingly found to be more effective in preventing or treating ischemia-reperfusion injuries than multiple low doses of NAC." (*See* specification as filed, page 16, lines 14-16.) Applicants submit that nowhere does Singh teach the use of a single high dose of a free radical scavenger in an amount sufficient for the serum concentration of the scavenger to be at least 1.5 mM for reducing ischemia/reperfusion injury in any organ, let alone a cerebral hemorrhage, or any injury in the brain resulting from pulmonary bypass surgery, nor does Singh

teach that a single high dose of free radical scavenger would be advantageous over low, continuous doses.

The teaching of Andersen does not overcome this deficiency. In particular, there is no actual teaching in Andersen that the administration of NAC at any dose is effective for reducing ischemia-reperfusion injury. Andersen merely describes the effect of NAC administered during pulmonary bypass surgery on the oxidative burst response of neutrophils. Andersen fails to cure the deficiencies of Singh in particular by providing no actual teaching with regard to the effect of the oxidative burst response of neutrophils on ischemia-reperfusion injury. While the reference suggests that this could have an effect on ischemia-reperfusion injury, there is no actual teaching of such. As would be recognized by the skilled artisan, while neutrophils may play a role, they are only one component of the post-cardiac surgery effect of free radicals. Moreover, Andersen even concedes, "The reduction in superoxide response in the presence of NAC may be consistent with a decreased cellular release secondary to the bypass procedure itself..." (emphasis added; see page 24, second column).

Thus, contrary to the PTO's assertion, Andersen does not teach that the administration of NAC (at any dose) *necessarily* reduces ischemia-reperfusion injury. In fact, Applicants have shown that the concentration of NAC used by Andersen, 100mg/kg, which may have the described effect on the oxidative burst response of neutrophils, is, in fact, too low to block free-radical damage either systemically or in the brain. Applicants submit that the Action employs inappropriate and selective hindsight where the allegation of obviousness is asserted to derive from a reason in the art other than knowledge provided by Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469; 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Absent the teachings of the present application, the documents cited in the Action simply fail to render the claimed invention obvious to the person having ordinary skill in the art, who would have no basis for reasonably believing that the instant methods could be successfully practiced.

In alleging that there would have been motivation to combine the references to arrive at Applicants' method of reducing an ischemia-reperfusion injury by administering a free radical scavenger in a single high dose in an amount sufficient for the serum concentration of the scavenger to be at least 1.5 mM, at best, the Action asserts nothing more than that it would have

been “obvious to try.” Such an assertion cannot be regarded as a conclusory finding that the claimed invention is obvious, and in fact fails to support a *prima facie* case of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943; 14 USPQ2d 1741 (Fed. Cir. 1990).

Applicants submit that the primary and secondary references, taken individually or for what they teach as a whole, do not teach or suggest the claimed invention. Therefore, Applicants submit that the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, the claims are now believed to be in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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